Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Trimethoxy(methyl)silane

EC Number: 214-685-0
CAS Number: 1185-55-3

CLH-O-0000001412-86-234/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

14 September 2018

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

Trimethoxy(methyl)silane

EC Number: **214-685-0**

CAS Number: **1185-55-3**

Index Number:

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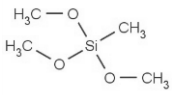
Version number: 2 **Date: 15 May 2017**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	trimethoxy(methyl)silane
EC number (if available and appropriate)	214-685-0
EC name (if available and appropriate)	Trimethoxy(methyl)silane
CAS number (if available)	1185-55-3
Molecular formula	C4H12O3Si
Structural formula	
SMILES notation (if available)	CO[Si](C)(OC)OC
Molecular weight or molecular weight range	136.22 g/mol
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Trimethoxy(methyl)silane (CAS 1185-55-3)	Not relevant	None	Current self-classification in the full/lead registration: Not sensitising --- In addition, the following hazard classes regarding skin sensitisation, irritation and acute toxicity (with frequency of occurrence) are notified among the 20 other aggregated self-classifications in the C&L Inventory: 2/20: Skin Sens 1 – H317 1/20: Skin Sens 1B – H317 6/20: Skin Irrit. 2 – H315 8/20: Eye Irrit. 2 – H319 3/20: STOT SE 3 – H335

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
			(respiratory sys.) 2/20: Acute Tox. 4 – H302 3/20: Acute Tox. 4 – H332

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Not relevant				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not relevant					

Information on the composition of the test substances is considered confidential, see confidential Annex I.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry											
Dossier submitters proposal		Trimethoxy(methyl)silane	214-685-0	1185-55-3	Skin Sens. 1B	H317	GHS07 Warning	H317	None	None	None
Resulting Annex VI entry if agreed by RAC and COM		Trimethoxy(methyl)silane	214-685-0	1185-55-3	Skin Sens. 1B	H317	GHS07 Warning	H317			

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Harmonised classification proposed	Yes
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no previous harmonised classification and labelling of Trimethoxy(methyl)silane.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Requirement for harmonised classification by other legislation or process.

Further detail on need of action at Community level

According to Article 36(3) of CLP Regulation for a substance that fulfills the criteria for other hazard classes or differentiations than those of CMR or respiratory sensitization (Category 1) and the substance is not an active substance regulated under the Plant Protection Product Directive (PPPD) and Biocidal Product Directive (BPD), a harmonised classification and labelling proposal can be submitted if a justification is provided demonstrating the need for such action at community level. Pursuant to Article 45(4) of the REACH Regulation the Member State Competent Authority (MSCA) of Sweden has initiated substance evaluation for trimethoxy(methyl)silane. In the course of the evaluation, the need for requesting further information to clarify skin sensitisation potential was considered. At a Member State Committee meeting (MSC 47), it was agreed that a proposal for harmonised classification and labelling for skin sensitisation under the CLP Regulation based on the available information should be submitted by MSCA of Sweden such that the Committee for Risk Assessment (RAC) may assess its applicability for CLP purposes (Minutes of the 47th Meeting of the Member State Committee (MSC-47)).

5 IDENTIFIED USES

Trimethoxy(methyl)silane is used in coating products, adhesives and sealants, textile treatment products and dyes, non-metal-surface treatment products, heat transfer fluids, polymers and semiconductors. The substance is used to manufacture other substances (as intermediate). It is manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tonnes per year.

6 DATA SOURCES

The Reach registration of Trimethoxy(methyl)silane and Chemical Safety Report (2016 update) were used to compile this CLH report. The unpublished full study reports were made available to MSCA Sweden by the lead registrant.

Searching of the ECHA database and the CLP (including ATPs) for registration dossiers of impurities related to classifications and self-classifications.

(Q)SAR Toolbox, Toxtree, VEGA and Danish QSAR database for structural alerts concerning protein binding and skin sensitisation potential of Trimethoxy(methyl)silane, methylsilanetriol and methanol.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Clear and colourless liquid.	REACH registration (ECHA 2016)	
Melting/freezing point	≤ -77 °C at 1 013 hPa	REACH registration (ECHA 2016)	
Boiling point	102 °C at 1 013 hPa	REACH registration (ECHA 2016)	
Relative density	0.95 g/cm³ at 25 °C	REACH registration (ECHA 2016)	
Vapour pressure	3000 Pa at 20°C	REACH registration	

Property	Value	Reference	Comment (e.g. measured or estimated)
		(ECHA 2016)	
Surface tension		Data waived in REACH registration (ECHA 2016)	
Water solubility	Water solubility of trimethoxy(methyl)silane: 91 000 mg/l (QSAR) Water solubility of the hydrolysis product methylsilanetriol: 1 000 000 g/L (QSAR)	REACH registration (ECHA 2016)	The requirement to test the substance for water solubility is waived on the basis that it hydrolyses rapidly to methylsilanetriol and methanol. The water solubility of both the substance and the silanol hydrolysis product have been calculated by the registrant using QSAR (EPI Suite).
Partition coefficient n-octanol/water	Log K_{ow} of trimethoxy(methyl)silane: 0.7 at 20°C (QSAR) Log K_{ow} of the hydrolysis product methylsilanetriol: -2.4 at 20°C (QSAR)	REACH registration (ECHA 2016)	The requirement to test the substance for octanol-water partition coefficient is waived because in contact with water the substance very rapidly hydrolyses to form methylsilanetriol. The log K_{ow} of the substance and its silanol hydrolysis product have been calculated by the registrant using QSAR (EPI Suite).
Flash point	7.7 °C at 101.3 kPa	REACH registration (ECHA 2016)	
Flammability		Data waived in REACH registration (ECHA 2016)	
Explosive properties		Data waived in REACH registration (ECHA 2016)	
Self-ignition temperature	Auto Flammability: 238°C at 1013 hPa	REACH registration (ECHA 2016)	
Oxidising properties		Data waived in REACH registration (ECHA 2016)	
Granulometry		Data waived in REACH registration (ECHA 2016)	
Stability in organic solvents and identity of relevant degradation products		Data waived in REACH registration (ECHA 2016)	
Dissociation constant		Data waived in REACH registration (ECHA 2016)	
Viscosity	0.5-0.6 mPa s (dynamic) at 25°C, 0.6 mm^2/s (static) at 25°C	REACH registration (ECHA 2016)	

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

The information below has been obtained from the sections on physicochemical properties and environmental fate in the REACH registration.

There are no data on the toxicokinetics of trimethoxy(methyl)silane. Trimethoxy(methyl)silane hydrolyses in contact with water (half-life approximately 2.2 hour at pH 7, <0.033 hours at pH 4, 0.11 hours at pH 9 and 25°C)), generating methylsilanetriol and methanol. Polyethylene glycol (PEG 300) was the vehicle in the skin sensitisation tests. Since hydroxide groups are present in PEG, hydrolysis can be expected but the half-life is unknown.

Due to rapid hydrolysis of the substance, the registrant has used QSAR (EPI Suite) to calculate water solubility and octanol-water partition coefficient. The estimated water solubility of trimethoxy(methyl)silane is 91 000 mg/l. The estimated Log K_{ow} of trimethoxy(methyl)silane is 0.7 at 20°C.

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

There are no data on the toxicokinetics of trimethoxy(methyl)silane. Trimethoxy(methyl)silane hydrolyses in contact with water generating methylsilanetriol and methanol. As PEG 300 was the vehicle used in the studies on skin sensitisation, it is likely that trimethoxy(methyl)silane would have hydrolysed and the animals are probably exposed to a mixture of trimethoxy(methyl)silane and the hydrolysis products but the equilibrium is unknown.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

Not evaluated in this dossier.

10.2 Skin corrosion/irritation

Not evaluated in this dossier.

10.3 Serious eye damage/eye irritation

Not evaluated in this dossier.

10.4 Respiratory sensitisation

Not evaluated in this dossier.

10.5 Skin sensitisation

Table 8: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results		Reference
Buehler OECD Guideline 406 (Skin Sensitisation) Induction: epicutaneous, occlusive Challenge: epicutaneous, occlusive Reliable	Guinea-pig, Dunkin-Hartley, males only, 20 treated males, 10 negative control males in group I, 10 negative control males in group II, 3 males in irritation screening I, 3 males in irritation screening II	Trimethoxy(methyl)silane Purity comparable to that of the REACH registration. Further detail in confidential Annex.	Induction: 50% in PEG 300 duration: 6 h Challenge: 25% in PEG 300 duration: 6h observation: 24 h and 48 h Re-challenge: 25% in PEG 300, and 15% in PEG 300 duration: 6h observation: 24 h and 48 h	Sensitising		Study report 2009
				Challenge:		
				Treated group, 25%, 24 h:	19/20 (95%)	
				Treated group, 25%, 48 h:	9/20 (45%)	
				Negative control, 25%, 24 h:	10/10 (100%)	
				Negative control, 25%, 48 h:	8/10 (80%)	
				Re-challenge		
				Treated group, 25%, 24 h:	6/20 (30%)	
				Treated group, 25%, 48 h:	4/20 (20%)	
				Negative control, 25%, 24 h:	0/10 (0%)	
				Negative control, 25%, 48 h:	0/10 (0%)	
				Treated group, 15%, 24 h:	0/20 (0%)	
				Treated group, 15%, 48 h:	0/20 (0%)	
				Negative control, 15%, 24 h:	0/10 (0%)	
				Negative control, 15%, 48 h:	0/10 (0%)	
Buehler OECD Guideline 406 (Skin	Guinea-pig, Dunkin-Hartley,	Trimethoxy(methyl)silane Purity unknown	Induction: 50% in PEG 300	Not sensitising		Study report

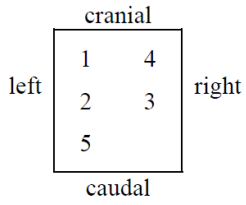
Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results		Reference
sensitisation) Induction: epicutaneous, occlusive Challenge: epicutaneous, occlusive Deviation: concentration for induction was not the highest to cause mild-to-moderate skin irritation Not reliable	male, 10 test males, 10 test females, 5 negative control males, 5 negative control females, 1 male and 2 females for irritation screening		duration: 6 h Challenge: 50% in PEG 300 duration: 6h observation: 24 h and 48 h	Challenge:		2013
				Test group, 50%, 24 h:	0/20 (0%)	
				Test group, 50%, 48 h:	0/20 (0%)	
				Negative control, 50%, 24 h:	0/10 (0%)	
				Negative control, 50%, 48 h:	0/10 (0%)	

Two Buehler tests are included in the lead REACH registration dossier of trimethoxy(methyl)silane. The general principle of the Buehler test according to OECD guideline 406 is that the test animals are initially exposed to the test substance by epidermal application using an occlusive patch or chamber (induction exposure). Following a rest period of 10 to 14 days (induction period), during which an immune response may develop in treated animals, the animals are exposed to a challenge dose using an occlusive patch or chamber. The extent and degree of skin reaction to the challenge exposure is compared with that demonstrated by control animals which undergo sham treatment during induction and receive the challenge exposure. The guideline states that the dose level selected for the induction exposure should be the highest to cause mild irritation. The concentration used for the challenge exposure should be the highest non-irritating dose (OECD Guideline 406, Skin sensitisation 1992).

Study report 2009

In the first Buehler test (Study report 2009), an irritation screening was conducted prior to the main study to determine the minimal irritation concentration of the induction period and the highest non-irritating concentration for the challenge and re-challenge periods. 0.5 mL of the test material was topically administered in a chamber. Dilutions weight/weight of trimethoxy(methyl)silane were freshly made throughout the study. All occlusive exposure durations were 6 hours. Moderate skin reactions (grade 2, moderate and confluent erythema) were observed with trimethoxy(methyl)silane applied undiluted topically. Topical administration with trimethoxy(methyl)silane at 75% in PEG 300, resulted in slight skin reactions (grade 1, discrete or patchy erythema), but with scaling. Trimethoxy(methyl)silane at 50% in PEG 300 produced slight skin irritation (grade 1), but without scaling, and therefore this concentration was selected for the epidermal induction period. The test item at 25% in PEG 300 did not result in a local skin reaction during irritation screening.

Formats for induction, challenge and re-challenge patch application, i.e. the main study, are presented below. The experiments on treated group and control group were run in parallel and in accordance with OECD test guideline 406.



1 = Induction (treated group with 50% of trimethoxy(methyl)silane in PEG 300 and the control group with PEG 300)

2 = Primary challenge (control and treated group with 25% of trimethoxy(methyl)silane in PEG 300)

3 = Primary challenge (control and treated group with PEG 300)

4 = Re-challenge (control and treated group with 25% of trimethoxy(methyl)silane in PEG 300)

5 = Re-challenge (control and treated group with 15% of trimethoxy(methyl)silane in PEG 300)

In the main study, twenty male guinea-pigs of the treated group was treated topically with trimethoxy(methyl)silane (with a purity comparable to the composition of the substance in the lead registration, for confidential information see Annex I) at 50% in PEG 300 once per week for a three week induction phase. Ten animals in the control group were treated in the same way as the test animals, but with the vehicle PEG 300 only. Two weeks after the final induction application, the control and treated animals were challenged with trimethoxy(methyl)silane at 25% in PEG 300 (left flank) and PEG 300 alone (right flank).

Table 9: Summary table of results from the first challenge on day 29 of study report 2009

The incidence of positive skin reactions after topical challenge with trimethoxy(methyl)silane at 25% in PEG 300 is summarised as follows:

Erythema Score	**Control Group I 10 animals**		**Trimethoxy(methyl)silane-treated Group 20 animals**	
	25%		**25%**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
0	0	2	1	11
1	10	8	17	9
2	0	0	2	0
3	0	0	0	0
4	0	0	0	0
No. with grades ≥1	10	8	19	9
No. tested	10	10	20	20
Incidence*	**10/10 (100%)**	**8/10 (80%)**	**19/20 (95%)**	**9/20 (45%)**
Severity**	1.0	0.4	1.05	0.45

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.
** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 4).

The results of the first challenge indicate an unspecific irritation reaction in treated and control animals, since the number of positive skin reactions are approximately the same in the control as in

the treated group, in combination with no positive reactions at 15% trimethoxy(methyl)silane in PEG 300. This reaction has not been explained in a satisfactory manner in the study, making the results less convincing. The irritation reaction could indicate that the chosen concentration was too high.

The right flank of both control and test group was treated with PEG 300 alone and all animals were devoid of any local signs at the observation time. The equivocal results prompted a re-challenge to clarify the results, as suggested by the OECD Guideline 406. A new irritation screening was performed, with three naïve guinea-pigs. No local skin reactions were observed at 25%, 15%, 10% and 5%. Therefore, the concentrations of 25% and 15% trimethoxy(methyl)silane in PEG 300 were chosen for the re-challenge period. A new control group II with 10 naïve male guinea-pigs were selected for the re-challenge while the treated group comprised of the same animals. The challenge was performed on test day 29 and the re-challenge was performed on test day 43. No signs of systemic toxicity were observed in any of the animals throughout the study.

Table 10: Summary table of results from the re-challenge on day 43 of study report 2009, at 25%

The incidence of positive skin reactions after topical challenge with trimethoxy(methyl)silane at 25% in PEG 300 is summarised as follows:

Erythema Score	**Control Group II 10 animals**		**Trimethoxy(methyl)silane-treated Group 20 animals**	
	25%		**25%**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
0	10	10	14	16
1	0	0	6	4
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
No. with grades ≥1	0	0	6	4
No. tested	10	10	20	20
Incidence*	0/10 (0%)	0/10 (0%)	**6/20(30%)**	**4/20 (20%)**
Severity**	0.0	0.0	0.3	0.2

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.

** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 4).

After topical challenge with trimethoxy(methyl)silane at 15% in PEG, the incidence of positive skin reactions was 0% for both treated animals and negative control.

Although the study report of 2009 initially gave equivocal results, the OECD guideline 406 states that a re-challenge can be performed if it is necessary to clarify the results obtained in the first challenge. Considering that trimethoxy(methyl)silane at 25% in PEG 300 was non-irritating in the two irritation screening experiments and also in the new control group II, the skin reactions observed in the test group in the first and second challenge when treated at 25% in PEG 300 would indicate the test item's skin sensitisation potential. Additionally, knowing that the sensitisation reaction is dose-dependent and local skin reactions were observed at the concentration of 25% trimethoxy(methyl)silane in PEG 300 while no local skin reactions were observed at the concentration of 15% trimethoxy(methyl)silane in PEG 300, the reactions are likely to be skin sensitisation when applied at 25% rather than irritation. The presence of skin reactions of grade 1 in

30% and 20% of the test animals after 24 and 48hr, respectively in the second challenge and absence of any evidence of irritation in control group II demonstrated the persistency of the limited skin reactions in the sensitised test animals.

The overall conclusion is that the result of the study report 2009 was positive and it was conducted according to OECD test guideline 406. Trimethoxy(methyl)silane shows limited potential to cause moderate skin sensitisation in guinea-pigs.

Study report 2013

In the second Buehler test (Study report 2013), an irritation screening was performed with three naïve guinea-pigs, one male and two females. The concentrations of trimethoxy(methyl)silane were at 50%, 25%, 15% and 10% dilutions in PEG 300. No skin reactions were observed at either concentration so the highest tested concentration, 50% trimethoxy(methyl)silane in PEG 300, was selected for induction phase. However, this is a deviation from the OECD guideline 406, as a concentration resulting in mild irritation should have been selected for induction and the highest non-irritating dose should be selected for the challenge.

For the main study, ten male and ten female guinea-pigs of the treated group was treated topically during the induction phase with trimethoxy(methyl)silane (with an unknown purity) at 50% in PEG 300 once per week for three consecutive weeks (day 0, 7 and 14). Five males and five females in the control group were treated in the same way as the test animals, but with the vehicle PEG 300 only. Two weeks after the final induction application, the control and test animals were challenged with the test item at 50% in PEG 300. On day 28, the challenge dose of 50% trimethoxy(methyl)silane in PEG 300 was administered on treated and naïve control animals. There is no information available if the preparations of the test substance was made fresh or not. No signs of toxicity were evident in any of the animals during the course of the study. No skin reaction scores were observed in any of the test animals or the negative control group after 24 or 48 hours.

Table 11: Summary table of results from the challenge of study report 2013

The incidence of positive skin reactions after topical challenge with trimethoxy(methyl)silane at 50% in PEG 300 is summarised as follows:

Erythema Score	**Control Group 10 animals**		**Trimethoxy(methyl)silane-treated Group 20 animals**	
	50%		**50%**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
0	10	10	20	20
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
No. with grades ≥1	0	0	0	0
No. tested	10	10	20	20
Incidence*	0/10 (0%)	0/10 (0%)	0/20 (0%)	0/20 (0%)
Severity**	0.0	0.0	0.0	0.0

*Number of animals showing a response of grade 1 or greater at either 24- or 48-hour reading out if the total animals.
** Total sum of 24- and 48-hour response readings divided by the number of animals exposed (maximum of 4).

The overall conclusion of the results of study report 2013 is that the study is negative, however the study is considered not reliable. The key points that has been considered when reaching this conclusion is firstly that the purity of the test substance has not been reported meaning that it is unknown whether or not enough trimethoxy(methyl)silane was present in the test material to be representative for the measurement of the substance's skin sensitisation potential. Secondly, the test procedure significantly differs from that described by the test method in OECD guideline 406 (that a concentration resulting in mild irritation should have been, but was not, selected for induction). These are a few of the key points considered when evaluating data reliability (ECHA Guidance on information requirements and chemical safety assessment 2011). In addition, it is not reported in the study if the test material was freshly prepared. Due to physicochemical properties, trimethoxy(methyl)silane will hydrolyse in water (half-life approximately 2.2 hour at pH 7 and 25°C). However, the rate of the hydrolysis in PEG 300 is unknown. The skin sensitisation potential of the hydrolysis products methylsilanetriol and methanol is unknown. No scientific justification has been provided why a higher concentration was not included in the irritation screening and selected for the induction when there was no skin reaction recorded in the screening. Although the study of 2013 might be a confirmatory study of the study of 2009, the OECD guideline 406 should have been followed. These limitations makes it difficult to scientifically assess if enough of trimethoxy(methyl)silane was present in the tested material, to draw the conclusion that the result is relevant for the substance for which CLH is proposed. In the irritation screening in the study of 2009, 75% of trimethoxy(methyl)silane could produce slight irritation with scaling and 50% could produce slight irritation without scaling, indicating that a suitable induction concentration might be between 75-50% of trimethoxy(methyl)silane if the testing conditions (including test material composition) are similar. Hence, a proper irritation screening could be crucial to establish a relevant induction concentration. The validity and relevance of the negative test result is questionable due to the above mentioned limitations.

A clear scientific explanation as to why the level of skin reaction differs has not been provided. A speculation is that the level of hydrolysis of trimethoxy(methyl)silane is involved, but there is no data to confirm this. pH seems to affect the rate of the substance hydrolysis in water which could also be true in PEG 300, however, there is no data to corroborate it. During substance evaluation, the evaluating MSCA identified a concern for mutagenic potential of trimethoxy(methyl)silane, which could be an indication of reactivity. To assess if there might be a difference in structural alerts which might explain a difference in irritation and skin sensitisation potential, trimethoxy(methyl)silane, methylsilanetriol and methanol were compared using QSAR ((Q)SAR Toolbox, Toxtree, VEGA and Danish QSAR database) by the Swedish Chemicals Agency. No differences were detected between the substance and the hydrolysis products regarding protein binding and skin sensitisation potential. However, the applicability of these models for silica molecules might be limited.

During the substance evaluation of trimethoxy(methyl)silane, there has been discussions on read across to other silanes in order to determine skin sensitisation. At MSC-47 it was agreed that a CLH dossier would be based on the current available dataset. The current Chemical Safety Report of 2016 does not elaborate on read across but is based on the current dataset. Consequently, read across to other silanes has not been considered necessary and has not been further evaluated in this dossier.

In conclusion, the study report of 2009 is reliable, it follows the OECD guideline 406 and it is performed with a test material of known purity. Due to the positive results of the re-challenge, the entire study is rendered positive.

Table 12: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Remarks	Reference
Summary	Trimethoxy(methyl)silane and mixtures containing	Secondary	During more than 20 years of production, handling and use of	The validity	Summary report

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Remarks	Reference
report	this substance	source	Trimethoxy(methyl)silane and mixtures containing this substance and during at least 14 years of external sale no single case of suspected contact allergy has been observed. Only acute slight redness, but no one case of skin sensitization has been observed. In addition, based on the experience of the plant managers (experience in production of this substance partially more than 20 years) and the application experts with direct relations to the customers there is no indication/information of sensitizing properties of trimethoxy(methyl)silane and of mixtures containing this substance. Furthermore, no other health effects have been communicated from the market.	and relevance of the information is unknown.	2013

Information on experiences from humans has been included from the REACH Registration for completeness. However, the information in the summary report is from a secondary source and does not contain data which can be interpreted. Hence, the validity and relevance is unknown.

10.5.1 Short summary and overall relevance of the provided information on skin sensitisation

A Buehler test (study report 2009), considered reliable, found that trimethoxy(methyl)silane caused skin sensitisation. At the first challenge, irritation reactions were observed in the negative control animals. To clarify the results, a second challenge (e.g. re-challenge) was performed, as recommended by the Buehler test OECD Guideline 406. After the re-challenge, discrete or patchy erythema was recorded in 30% of the animals treated with 25% trimethoxy(methyl)silane in PEG 300 at the 24 hours reading. 48 hours later, the skin reaction was still evident in 20% of the animals treated with 25% trimethoxy(methyl)silane in PEG 300. No skin reactions were detected at re-challenge in the naïve negative control animals. Taken together the entire study was considered positive. Trimethoxy(methyl)silane exhibited a moderate skin sensitisation potency.

In a second Buehler test (study report 2013), found to be not reliable, trimethoxy(methyl)silane did not cause skin sensitisation. The selected concentration for induction did not cause mild-to-moderate skin irritation in the irritation screening, as is required by the Buehler test OECD Guideline 406. In addition, the purity of the tested substance has not been reported. The validity and relevance of the negative test results is questionable due to the limitations of the study.

It is noted that the study of 2013, which found the test material not sensitising, used a higher concentration of test substance (50% at induction and challenge doses), than the study of 2009 which concluded the test substance to be a sensitiser (50% at induction and 25% at re-challenge doses).

However, the negative study of 2013 is considered to be not reliable due to the OECD guideline 406 deviation making the test procedure not entirely in accordance, the reporting of purity and the availability of the raw data (as specified in ECHA Guidance on information requirements and chemical safety assessment 2011). Moreover, negative results does not negate the positive results of the study from 2009.

The human data (summary report 2013) is not considered relevant for the purpose of assessing skin sensitisation potential of trimethoxy(methyl)silane under CLP, as this is only a summary report from a secondary source.

10.5.2 Comparison with the CLP criteria

Substances are classified as skin sensitisers Category 1 if there is evidence in humans, or if there are positive results from an appropriate animal test. Test results from the Buehler test can be used for potency evaluation. For Category 1, when a non-adjuvant Guinea pig test method is used, a response of at least 15 % of the animals is considered positive.

Sub-category 1B include substances showing a low to moderate potency in animals, which can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.

Criteria for skin sensitisation from animal test results for sub-category 1B can include data with the below indicated values, according to the CLP Regulation (Table 3.4.4)

Table 13: Study results in comparison with CLP criteria

Assay	Criteria
Buehler assay	≥ 15 % to < 60 % responding at > 0,2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose

In the study report of 2009, the result was 30% of the animals responding at the 24 h observation and 20% at the 48 h observation with the topical induction dose of 50% trimethoxy(methyl)silane in PEG 300.

10.5.3 Conclusion on classification and labelling for skin sensitisation

Trimethoxy(methyl)silane is fulfilling the CLP criteria to be classified for skin sensitisation, sub-category 1B. Although initially an unexplained irritation reaction occurred in the positive study report from 2009, the study is acceptable and reliable as a re-challenge may be performed to clarify the results according to the OECD Guideline 406 and those findings were positive. It is not considered necessary to set a specific concentration limit.

RAC evaluation of skin sensitisation
Summary of the Dossier Submitter's proposal The dossier submitter (DS) has provided the results of two *in vivo* skin sensitisation studies of trimethoxy(methyl)silane (TMMS) in guinea pigs conducted according to the

Buehler protocol and, additionally, existing human data.

Animal data

The first Buehler test (study report, 2009) was performed according to OECD TG 406 (EU Method B.6) and in compliance with GLP. Purity of tested TMMS was 96.4 ± 0.2%.

An irritation screening was conducted prior to the main study to determine the mild-to-moderate irritating concentration for the induction and the highest non-irritating concentration for the challenge and re-challenge. Topical administration of TMMS at 75% in PEG 300 (polyethylene glycol of average molecular weight 300) as vehicle, resulted in slight skin reactions (grade 1, discrete or patchy erythema) with scaling. TMMS at 50% in PEG 300 produced slight skin irritation (grade 1), but without scaling, and therefore this concentration was selected for the epidermal induction period. TMMS at 25% in PEG 300 did not result in a local skin reaction during irritation screening.

In the main study the following concentrations of TMMS in PEG 300 were used: 50% for the epidermal induction period (6 hours exposure) applied once per week for three consecutive weeks of induction phase, 25% for challenge and re-challenge, 15% in PEG 300 was used additionally for re-challenge.

The animals in the control group, during induction phase, were treated with the vehicle PEG 300 only. Two weeks after the final application for induction, the control and treated animals were challenged with TMMS at 25% in PEG 300 (left flank) and PEG 300 alone (right flank).

The results of the first challenge (see table below) indicate an unspecific irritation reaction in treated and control animals because the number of positive skin reactions were approximately the same in the control as in the treated group. No positive reactions were seen in the re-challenge using 15% TMMS in PEG 300. The possible reasons for these skin reactions have not been explained in the study, making the results difficult to interpret. The irritation reaction could indicate that the chosen concentration was too high.

The re-challenge was performed to clarify the results obtained in the first challenge (as suggested by the OECD TG 406). A new irritation screening study was performed, with three naive guinea-pigs for each concentration tested. No local skin reactions were observed at 25%, 15%, 10% and 5%. Therefore, the concentrations of 25% and 15% TMMS in PEG 300 were chosen for the re-challenge. A new control group II with 10 naive male guinea-pigs were selected for the re-challenge while the treated group comprised of the same animals.

100% of control animals had positive skin reaction 24 h after first challenge with 25% TMMS in PEG 300, while after 48 h 80% of control animals had positive skin reaction. The percentage of animals with positive skin reaction in the treated group of animals was 95% and 45% after 24 and 48 h, respectively.

Considering that TMMS at 25% in PEG 300 was non-irritating in the two irritation screening experiments and also in the new control group II, the skin reactions observed in the test group in the first and second challenge, when treated at 25% in PEG 300, where recognised by the DS as skin sensitisation responses to the test material.

The presence of skin reactions of grade 1 in 30% and 20% of the test animals after 24 and 48 h, respectively, in the second challenge and, absence of any evidence of irritation

in control group II, demonstrated consistency in the ability to cause limited skin reactions in the treated animals indicating weak skin sensitisation. Additionally, the DS considered these reactions, after application of TMMS at 25%, as likely to be skin sensitisation rather than irritation, given that the sensitisation reaction is dose-dependent and local skin reactions were observed at the concentration of 25% TMMS in PEG 300, while no local skin reactions were observed at the concentration of 15% TMMS in PEG 300.

The overall DS's conclusion was that the result of the first Buehler test (study report 2009) was positive and TMMS showed limited potential to cause moderate skin sensitisation in guinea-pigs.

The second Buehler test (study report, 2013), was performed according to OECD TG 406 (EU Method B.6) and in compliance with GLP. Purity of tested TMMS was reported by DS as unknown but was clarified and amended to be 99.6% in March 2018 study report, 2013.

An irritation screening was performed with the following dilutions of TMMS in PEG 300: 50%, 25%, 15% and 10%. No skin reactions were observed at either concentration so the highest tested concentration, 50% TMMS in PEG 300, was selected for the epidermal induction period (6 hours exposure) and challenge. However, this is a deviation from the OECD TG 406, as a concentration resulting in mild irritation should have been selected for induction and the highest non-irritating dose should be selected for the challenge.

No signs of toxicity were evident in any of the animals during the course of the study. No skin reaction scores were observed in any of the test animals or the negative control group 24 or 48 hours after challenge.

The overall DS's conclusion of the results of study report 2013 is that the study is negative, however the study is considered by DS as not reliable. The key points that has been considered when reaching this conclusion is firstly that the purity of the test substance has not been reported. Secondly, the test procedure significantly differs from that described by the test method in OECD TG 406 (that a concentration resulting in mild irritation should have been selected for induction, but was not). These are key points considered when evaluating data reliability (ECHA Guidance on REACH information requirements and chemical safety assessment, 2011). No scientific justification has been provided why a higher concentration was not included in the irritation screening and selected for the induction when there was no skin reaction recorded in the screening. However, since the authors of the second Buehler test knew the results of the first Buehler test, they could expect that TMMS already at concentrations 25 and 50% would be causing skin irritation, which was not confirmed in second skin irritation screening test.

It should be noted that due to physicochemical properties, TMMS hydrolyses in water (half-life approximately 2.2 hour at pH 7 and 25°C). However, the rate of the hydrolysis in PEG 300 is unknown. The skin sensitisation or skin irritation potentials of the hydrolysis products methylsilanetriol and methanol are unknown.

Human data

In the REACH registration dossier (summary report, 2013, ECHA dissemination) it is reported that during more than 20 years of production, handling and use of TMMS and mixtures containing this substance and during at least 14 years of external marketing no

single case of suspected contact allergy has been observed. Only acute slight redness, but no cases of skin sensitization has been observed.

In addition, it is also reported that, based on the experience of the plant managers (experience in production of this substance partially more than 20 years) and the company staff with direct relations to the customers, there is no indication/information of sensitizing properties of TMMS and of mixtures containing this substance. Furthermore, no other health effects have been communicated from the market.

In summary, TMMS was considered by the DS as skin sensitiser sub-category 1B based on positive results of a Buehler test (study report, 2009). Discrete or patchy erythema was recorded in 30% of the animals treated with 25% TMMS in PEG 300 at the 24 hours reading. 48 hours later, the skin reaction was still evident in 20% of the animals treated with 25% TMMS in PEG 300.

Comments received during public consultation

Two MSCAs did not agree with the proposed harmonised classification as Skin Sens. 1B; H317, based on the results of study report, 2009. These MSCAs questioned the relevance of this study considering the positive responses (100%) reported in the control group at the first challenge. One of this two MSCA noted that a new study would be useful to clarify this endpoint.

One Company-Manufacturer requested to take into account in the assessment of the skin potential of TMMS that:

- findings in the test group after re-challenge (study report, 2009) are unspecific reactions due to irritation
- good reliability of study report 2013 taking into account information from study owner (study report, 2013 amended in March 2018)
- existing and available information from human on skin sensitisation potential of TMMS

This company provided the following clarification on human data (summary report, 2013):

1. The following sources have been used to evaluate the skin sensitization potential of TMMS:

- Company internal data: relevant plants, number of employees, exposure description; medical surveillance
- Company internal regular health checks (especially concerning skin status) already performed on employees of the relevant plants
- Information from the Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies
- Information from Employer's liability insurance association (BG Bau)
- Information from customer
- Comprehensive literature search

2. Concerning the exposure situation, company internal experience and REACH dossier data have been summarized.

During more than 20 years of production (> 1000 t/a; two production sites), handling and use of TMMS and mixtures containing this substance in several of the company production sites and during at least 14 years of external sale no single case of suspected contact allergy has been observed/reported. No signs of skin sensitization have been observed by the medical doctors and no skin disorders have been reported by the concerned employees during the regular health examinations, which comprise the Occupational Medical Examination "Skin disorders (not including skin cancer)". In total, 855 medical check-ups of 168 employees have been performed. Relevant exposure can be expected during this time (20 years for production staff and 14 for sale).

Information from other sources described above leads to the same conclusion. No case of skin sensitization has been observed and no such case has been reported in the scientific literature.

Assessment and comparison with the classification criteria

The skin sensitisation potential of TMMS has been assessed in two Buehler tests. A study from 2009 performed with TMMS of purity 96.4 ± 0.2% and a study from 2013 with TMMS with a purity of 99.6% (study report, 2013 as amended in March 2018). Thus, purity of tested substance was higher in the test from 2013. In both studies, fresh preparation of solution in PEG 300 was made for each day of application in the main study (as clarified in the amendment of study report, 2013), therefore the possibility of hydrolysis of TMMS in PEG 300 is the same in both tests.

The first Buehler test (study report, 2009)

Based on an irritation screening study (25%, 50%, 75% and 100% TMMS in PEG 300) 50% TMMS, as the highest mildly irritant dose, was used for the skin sensitisation induction, and 25% TMMS, as the highest non-irritating dose, was used as challenge dose. 24 h and 48 h after first challenge 95% and 45% of the test animals had positive reactions in treated group, respectively. However 100% and 80% of the test animals had positive reactions in control group 24 h and 48 h after first challenge.

The results of the first challenge indicate an unspecific irritation reaction in treated and control animals, since the frequency of positive skin reactions were approximately the same in the control and in the treated group. This reaction has not been explained in a satisfactory manner in the study. The irritation reaction could indicate that the chosen concentration was too high.

Re-challenge was performed to clarify the results obtained in the first challenge. A new control group II with 10 naive male guinea-pigs were selected for the re-challenge while the treated group comprised of the same animals.

24 h and 48 h after topical re-challenge with TMMS at 25% in PEG 300, 30% (6/20) and 20% (4/20) of the test animals had positive reactions in treated group and absence of any evidence of irritation in new control group II.

After topical re-challenge with TMMS at 15% in PEG, the incidence of positive skin reactions was 0% for both treated animals and new negative control.

Table: *The results of first Buehler test (study report, 2009)*

	Control Group 10 animals		**Trimethoxy(methyl)-silane-treated Group (induction phase with 50%) 20 animals**	
	24 h	**48 h**	**24 h**	**48 h**
Primary challenge 25% on test day 29	***Control group I***		19/20 (95%)	9/20 (45%)
	10/10 (100%)	8/10 (80%)		
Re-challenge 25% on test day 43	***Control group II***		6/20 (30%)	4/20 (20%)
	0/10 (0%)	0/10 (0%)		
Re-challenge 15% on test day 43	***Control group II***		0/20 (0%)	0/20 (0%)
	0/10 (0%)	0/10 (0%)		

The second Buehler test (study report, 2013)

An irritation screening was performed (50%, 25%, 15% and 10% dilutions of TMMS in PEG 300). No skin reactions were observed at any of the concentrations so the highest tested concentration, 50% TMMS in PEG 300, was selected for induction and challenge phase. However, this is a deviation from the OECD TG 406, as a concentration resulting in mild irritation should have been selected for induction and the highest non-irritating dose should be selected for the challenge.

No signs of toxicity were evident in any of the animals during the course of the study. No skin reaction scores were observed in any of the test animals or the negative control group after 24 or 48 hours.

Human data

No TMMS human patch test are available, the 'negative' human data consist of the reporting of 'no cases observed/reported' in a few companies. The absence of cases of skin sensitisation may be due to absence of a sensitising potency of TMMS or due to low/absent exposure. The highest dermal exposure for workers reported in the registration dossier is 0.11 mg/kg bw/d, with 240 cm^2 exposed area. This converts to approximately 0.03 mg TMMS/cm^2 (0.11 * 60 kg : 240 cm^2). Compared to the exposure in the Buehler test (assuming a liquid layer of 0.5 mm, which equals 0.05 cm^3 liquid/cm^2 or 50 mg liquid/cm^2, and accounting for a 50% test concentration, the exposure is 25 mg TMMS/cm^2), the worker exposure is much lower than the exposure in the Buehler test. So, the absence of skin sensitisation in workers can most likely be explained by the low exposure levels and can therefore not be used to justify the absence of a skin sensitising potential.

Comparison with the classification criteria

The first Buehler study (2009) is considered as having low reliability due to high incidence of skin responses in the first challenge in the negative control group, inconsistency of results between the challenge and the re-challenge at the same concentration, so the results were considered equivocal and not providing sufficient evidence for classification.

In the second Buehler study (2013) the concentration chosen for induction (50%) may have been too low since it did not caused mild skin irritation in the screening and in the

main study, thus not conforming to the requirement of OECD TG 406 that the tested concentration should be the highest inducing mild irritation.

However, the absence of skin sensitisation in workers cannot be regarded as an evidence of lack of sensitising properties of TMMS, since the number of exposed workers and the dermal exposure level were low.

Overall, all the available information is of limited reliability and in combination does not allow a conclusion on the skin sensitising potential of TMMS. Therefore, RAC is of the opinion that **TMMS should not be classified as skin sensitiser due to inconclusive data.**

10.6 Germ cell mutagenicity

Not evaluated in this dossier.

10.7 Carcinogenicity

Not evaluated in this dossier.

10.8 Reproductive toxicity

Not evaluated in this dossier.

10.9 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.10 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier.

10.11 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

12 REFERENCES

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13 ANNEXES

Annex I – Confidential information on compositions and impurities.